REMARKS

The Office Action has been carefully reviewed. No claim is allowed. Claims 5, 9, 11, 12 and 15-17 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

New dependent claim 19 is supported by the specification at page 9, lines 13-15.

Claims 5, 9, 11, 12 and 15-18 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. This rejection is respectfully traversed.

Applicants indicate that one of their findings is that leptin induces angiopoietin 2, a receptor antagonist that acts on endothelial cells - namely cells that build the inner wall of blood capillaries and vessels. The activity of this antagonist depends on the environment and specifically, on VEGF levels. In the presence of sufficient VEGF, leptin-induced Ang2 will help to expand blood vasculature since the first step in blood vessel expansion requires some remodeling of the existing blood vasculature (observed as "fenestration"). This is what all the prior art cited by the examiner measured and reported.

Applicants' findings however relate to situations where VEGF is not present in sufficient concentrations. Under such conditions, leptin inhibits endothelial cell proliferation

and hence new blood vessel formation. This is what is now claimed.

The use of ob/ob mice as an *in vivo* model is convenient since the leptin background is zero. Clearly, the intent is to treat patients and/or tissues of patients with normal levels of leptin, but the ob/ob model is simply more convenient for observing the effects of leptin. Applicants do not understand why the examiner has a preference for one *in vivo* model over another. Once again, the use of ob/ob mice was intended only to avoid the background of endogenous leptin. Regarding the experiments in the references cited by the examiner, another examiner or another person of ordinary skill in the art could well take the position that implantation of leptin in the cornea is an artificial system since leptin is not normally found in the cornea. It is of course produced and is present in adipose tissue.

The examiner cites and applies references showing that implanting pellets saturated with leptin in the cornea of rats or in the chorioallantoic membrane of a chick embryo induces angiogenesis (Sierra-Honigmann 1998; Bouloumie, 1998, Cao, 2001). These results were further supported by some *in vitro* studies. The examiner also mentioned capillary leakage (fenestration) *in vivo* in mice upon administration of leptin (Cao, 2001). Such

leakage however is not synonymous with capillary proliferation and obviously can occur following destruction of capillary walls.

Applicants have demonstrated that administration of leptin to ob/ob mice led to induction of Ang-2 *in vivo* in adipose tissue without induction of VEGF. Such induction of Ang-2 leads to apoptosis of endothelial cells. Indeed, this is what applicants found in the adipose tissue of ob/ob mice *in vivo*. Since endothelial cells make the capillary wall, their apoptosis means the elimination of capillaries. One may endlessly argue the suitability of one *in vivo* model over the other. For example, one could conclude from one model that leptin induces angiogenesis only in the cornea since it was not tested in other tissues. So far, leptin has not been identified in chicken, rendering the model of chorioallantoic membrane of a chick embryo questionable. Clearly, administration ip is a practical means of administration, whereas corneal implantation is used only in experimental biology.

Applicants submit that the description of the present application does not teach only an *ob/ob* mouse where leptin inhibits angiogenesis. The present specification provides evidence for the angiostatic effect of leptin, notably on adipose cells:

- The specification, page 3 lines 16-17, teaches that Ang-2 is expressed upon blood vessel regression.

- Figure 4, shows the effect of leptin on the expression of Ang-2 in adipose tissue, in a normal mouse (line 3) and in a ob/ob mouse (line 5).
- Example 2 states that ". . . the injection of leptin induced the expression of Ang-2 in both types of mice (Figure 4). These results demonstrate that leptin is a potent inducer of the angiostatic factor Ang2" (page 25, lines 22-24).
- Figure 7 shows that leptin induces the expression of ang-2 in normal cultured adipocytes.
- Example 3 (based on Figure 7) discloses that "...these results suggest that leptin induces an angiostatic signal in mature adipocytes..." (page 28, lines 3-4).
- This information demonstrates that the use of leptin increases the expression of Ang-2 in adipose cells (normal or *ob/ob*) and that such increase in ang-2 level leads to blood vessel regression, induces an angiostatic signal in adipose cells (inhibition of angiogenesis in adipose tissue).

There is no problem of inherency between the prior art cited in this enablement rejection (as support for the examiner's position) and the present invention. The big difference is that the present invention shows that leptin has an angiogenesis

inhibitory effect in adipose tissue, as now positively recited in the present claims.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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